

Eighty years after insulin: parallels with modern islet transplantation

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This year marks the 80th anniversary of the publication in *CMAJ* of the discovery of insulin by Frederick Banting and his colleagues at the University of Toronto.¹ Some interesting historical parallels have emerged with the success of islet replacement therapy in diabetes. Up until just a few weeks ago, human islet cells were being prepared in the very same basement laboratories at the University of Alberta where the biochemist James Bertram Collip once worked on ethanol extraction of insulin, before he moved to Toronto and joined Banting's team (Fig. 1).²

The original process used to extract insulin is analogous to the complex extraction process used today to prepare islets for transplantation from scarce cadaveric pancreata. In fact, our work is foreshadowed in an entry in Banting's notebook on June 9, 1921, in which he documents a detailed experimental plan to study transplantation of non-vascularized grafts of the pancreas in dogs, placed either "free in the peritoneum" or "subcutaneously" or prepared as a nonpurified "emulsion" analogous to the preparation of islets for transplantation today (Fig. 2).² Banting was not the first to explore the concept of cellular replacement therapy in diabetes. Von Mering and Minkowski treated a diabetic dog with subcutaneous fragments of its own pancreas in 1892.³ A remarkable case report published in the *British Medical Journal* in 1894, 27 years before the discovery of insulin, describes the attempt by Watson-Williams and Harsant to treat a 13-year-old boy dying from ketoacidosis with subcutaneous implants of a sheep's pancreas; they noted temporary improvement in glycosuria before the boy rejected the xenograft and died 3 days later.⁴ In 1916, Pybus carried out similar clinical studies in Newcastle, England, but used subcutaneous implants of fragments of a human cadaveric pancreas.⁵

The modern procedure for implantation of islets is simple and relatively noninvasive. It is carried out without surgery under local anesthetic using fluoroscopic guidance. Islets are implanted into the portal vein where they embolize to the liver, nest and develop a new blood supply. The procedure is often completed as a day case, with patients discharged from hospital in less than 24 hours.

Clinical outcomes for islet transplantation were transformed in 2000 with the introduction of the Edmonton Protocol; a series of 7 consecutive patients with type 1 diabetes mellitus were all rendered insulin independent after



Fig. 1: Jonathan Lakey, Ray Rajotte, James Shapiro, Tatsuya Kin and Deborah McGhee-Wilson at work in the basement laboratory at the University of Alberta where the biochemist J.B. Collip worked before he joined Frederick Banting's team and contributed to the discovery of insulin.

receiving an average of 850 000 islets.⁶ The success of this protocol has been attributed to the use of potent antirejection therapy without corticosteroids, combined with delivery of a sufficient number of high-quality islets prepared from an average of 2 donor organs. The preparation of islets from a cadaveric pancreas is a complex and demanding process that takes 4 technicians up to 7 hours to complete. A number of institutions worldwide have collaborated in the evolution of the techniques. Collagenase enzyme is pumped down the pancreatic duct in a controlled perfusion system designed to cleave islets from their acinar restraining matrix.⁷ The pancreas is then chopped into pieces and transferred to a recirculating Ricordi digestion chamber.⁸ After extensive washing, islets are purified on a continuous Ficoll density gradient in a cell apheresis cen-

trifuge system.^{9,10} The process remains labour intensive and the efficiency of the isolation can sometimes be quite variable, depending on the quality of the procured pancreas and the nature of the particular batch of collagenase enzyme. The process yields sufficient islets for transplantation on approximately 50% to 75% of occasions. The parallels between the islet isolation techniques used today and the original techniques used to prepare insulin are striking, and inevitably our techniques will be further refined and greatly improved in efficiency over time.

The discovery of insulin and its introduction into clinical practice remains perhaps the most remarkable advance in the history of medicine. In the early days, the almost-instant salvation from rapid wasting and inevitable death from diabetes to a life invigorated by insulin injections must have turned tears to joy for countless patients, families and their physicians around the world.² One cannot help but reflect on the tough ethical dilemmas that physicians and hospital committees must have faced in trying to choose which of their desperately needy patients would receive the first precious vials of insulin. Parallels exist for islet transplantation today. Within weeks of the publication of the Edmonton Protocol in June 2000,⁶ over 5000 patients from around the world referred themselves to the islet program in Edmonton, jamming the hospital switchboard for days. Four thousand of these patients came from the United States or abroad and were turned away to ensure that Canadian organs were distributed fairly to Canadian patients.

Over 40 Canadian patients have now been treated at the University of Alberta, and 82% of them have maintained independence from insulin at the 1-year mark. Stringent enrolment criteria are used to pick the patients who are at greatest risk: selection has been based on the presence of recurrent severe hypoglycemic comas or marked glycemic lability in most cases, and occasionally on the presence of early but progressive secondary diabetic complications that fail to stabilize with intensive insulin therapy. Recurrence of autoimmunity or rejection has occasionally led to complete graft loss, but the antirejection therapy has prevented this in most cases. The majority of grafts continue to function and maintain insulin independence beyond 3 years, but longer term outcomes and the impact of islet transplantation on secondary complications of diabetes remain under active review.^{11,12}

The Edmonton Protocol and a number of recent variants, including 2-layer pancreas preservation, islet culture and other nonsteroidal immunosuppressant strategies, have now been replicated in over 15 islet transplant centres involving over 160 patients worldwide, and a multicentre international trial is currently focused in 9 of these centres, funded by the Immune Tolerance Network. The treatment is not risk free: complications have included partial thrombosis of the portal vein in less than 2% of cases, and bleeding requiring blood transfusion in approximately 5% of cases. More frequent complications include mouth ulcera-

tion, worsening of hypertension or elevation of cholesterol resulting from antirejection therapy.¹²

Eighty years after the discovery of insulin, which is the better treatment for type 1 diabetes mellitus: an islet transplant or injected insulin? In theory, islets are better than insulin because islets secrete their insulin internally with a near-perfect physiological response to a meal challenge and are thereby more able to regulate glucose in the normal range, without risk of overdosage and hypoglycemia. Intensive insulin therapy improves but rarely normalizes glycated hemoglobin levels.¹³ Cumulative evidence from whole pancreas transplantation indicates that near-perfect glycemic control after successful transplantation can prevent, stabilize and occasionally reverse most of the secondary complications of diabetes. Islet transplantation offers a similar potential, provided that graft function can be sustained over time.¹¹ In theory, an islet transplant could function for the entire lifetime of the patient, as long as immunological damage from recurrence of autoimmunity or allograft rejection is prevented. The patient who has maintained islet function for the longest period to date received a transplant of her own islets after total pancreatectomy at the University of Minnesota over 16 years ago and she remains insulin independent.¹⁴

Expansion of islet transplantation activity worldwide may remain limited for some time to come, for a number of reasons. First, islet isolation facilities are not yet available at most institutions. Second, the methods required to isolate and purify islets are complex and require a steep learning curve.¹⁵ Third, state-of-the-art isolation facilities meeting current and future good manufacturing practice standards are prohibitively expensive to develop (regional commercial islet isolation resource centres may be favoured in the

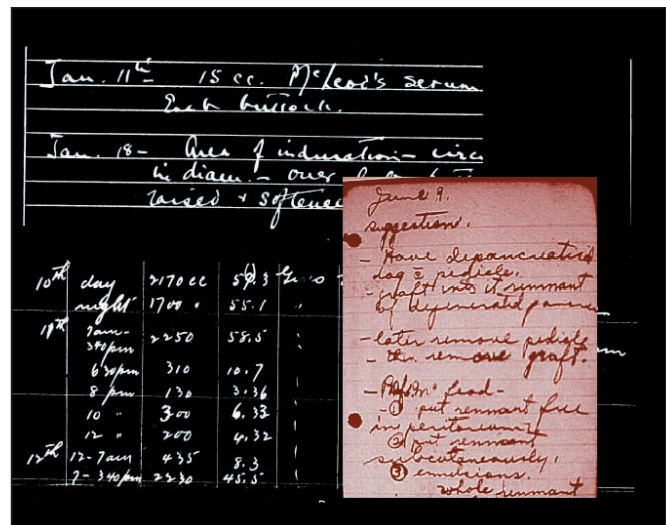


Fig. 2: In an entry in his notebook on June 9, 1921, Banting described his experimental plan for preparing emulsions of pancreatic tissue for transplantation: "Have depancreatised dog with pedicle. Graft into it remnant of degenerated pancreas. Later remove pedicle. Then remove graft."

longer run to justify the expense). Fourth, to secure insulin independence with an islet transplant, 2 cadaveric donors are usually required to provide a sufficient islet engraftment mass, except in highly selected recipients with low body weight and insulin requirements. Fifth, the costs of an islet transplant procedure (approximately \$70 000) and antirejection medications (approximately \$30 000 in the first year) are considerable. Cost-utility data may help justify the exchange of insulin for immunosuppression; in 2001, Canada spent approximately \$14 billion on diabetes and its complications.¹⁶

The status of islet transplantation today is therefore analogous in some respects to the status of insulin 80 years ago. The current limitations of islet transplantation may prove to be much tougher problems to solve, however, than those associated with the mass extraction of insulin in 1923. The severely limited supply of cadaveric pancreata means that of the 200 000 patients with type 1 diabetes mellitus in Canada today, fewer than 0.5% will be treated with islet transplantation with current technologies. Means to improve the efficiency of the islet isolation process, treatments to proliferate islets in vitro or after implantation in patients, approaches to facilitate islet transplants from living donors (possibly using a laparoscopic approach to remove the distal third of the pancreas) and, ultimately, alternative cell source strategies including stem cell and xenotransplantation all offer exciting promise. If strategies to induce graft tolerance or to achieve more rapid graft accommodation more safely prove to be successful, islet transplantation will be initiated earlier in the course of the disease, perhaps even at diagnosis, and will be available to children.

Although islet transplantation has provided a bright light at the end of the tunnel for many patients with diabetes and their families and has offered much hope that a cure may be closer, major challenges lie ahead. Insulin will remain the mainstay therapy in diabetes for some time to come.

Banting ended his 1923 Nobel laureate speech as follows: "Insulin is not a cure for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrates, so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life."¹⁷ If he were around today, Banting would no doubt

note that 80 years on from insulin, even islet transplantation "is not a cure for diabetes; it is a treatment." The transition from treatment to cure will take a concerted effort by teams of skilled scientists around the globe. Until a cure for diabetes is found, the Flame of Hope outside Banting House in London, Ontario, will burn on.

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